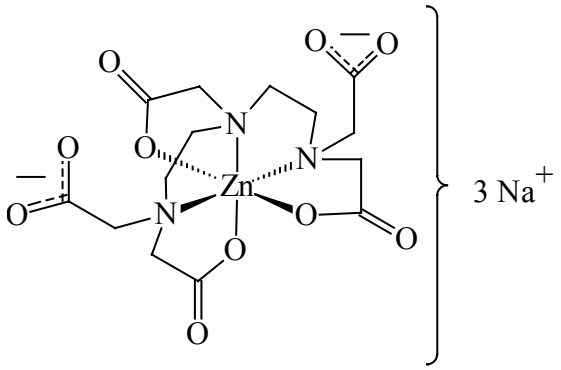
[Insert tradename _____]
Zn-DTPA (*pentetate zinc trisodium injection)*

For Intravenous Administration

DESCRIPTION

Pentetate zinc trisodium is the sodium salt of zinc diethylenetriaminepentaacetate. The pentetate zinc trisodium is also known as trisodium zinc diethylenetriaminepentaacetate and is referred to as Zn-DTPA. It has a molecular formula of $Na_3ZnC_{14}H_{18}N_3O_{10}$ and a molecular weight of 522.7 daltons. The drug is supplied as 1 grams of complex in 5 ml of sterile aqueous solution. [*Insert any inactive ingredients*] The structural formula is shown below.



CLINICAL PHARMACOLOGY

General

Zn-DTPA forms stable chelates with metal ions by exchanging zinc for a metal of greater binding capacity. DTPA has a very high affinity for certain transuranium radioactive elements (e.g., plutonium, americium, curium, berkelium and californium). The radioactive chelates are then excreted by glomerular filtration into the urine.

Zn-DTPA forms less stable chelates with uranium and neptunium *in vivo* resulting in deposition of these elements in tissues including the bone in animal studies. Zn-DTPA treatments are not expected to be effective for uranium and neptunium. Radioactive iodine is not bound by DTPA.

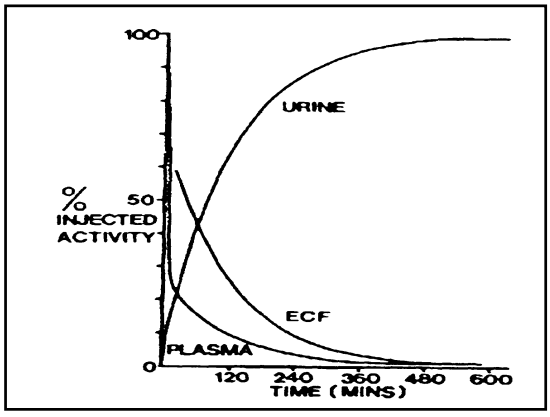
Pharmacodynamics

In a study of rodents after exposure to plutonium, the rate of plutonium elimination was measured after treatment with Ca-DTPA and Zn-DTPA given intravenously as a single dose of 10 to 1,000 μmol/kg (0.54 – 54 x MHD). In this study, when treated within one hour of plutonium exposure, in comparison to Zn-DTPA, treatment with Ca-DTPA resulted in about a 10 fold higher rate of urinary chelate elimination. The chelating capacity of Ca-DTPA is greatest immediately and up to approximately 24 hours after plutonium exposure when the radioisotope is still circulating and readily available for chelation. After the first dose of Ca-DTPA, maintenance treatment with either Ca-DTPA or Zn-DTPA resulted in similar rates of radiation elimination. However, at comparable doses, Zn-DTPA had less toxicity (e.g., less depletion of trace metals, lower rate of mortality, the absence of kidney and liver vacuolization, and absence of small bowel hemorrhagic lesions). The amount of Zn-DTPA chelation is dependent not only on the transuranium element, but also on the chemical and physical characteristics of the transuranium compound at the time of Zn-DTPA administration. The effectiveness of chelation decreases with time after contamination because the transuranium elements become incorporated into the tissues. Chelation treatment should be given as soon as possible after known or suspected transuranium element contamination has occurred. (See **WARNINGS** and **DOSAGE ADMINISTRATION**.)

Pharmacokinetics

Plasma retention and urinary excretion data were obtained in 2 patients that received 750 kBq of ^{14}C-DTPA. As shown in figure 1, the radiolabeled DTPA was rapidly distributed through the extracellular space and was cleared by glomerular filtration. The plasma retention up to 7 hours post dosing was expressed by the sum of three exponential components with average half-lives of 1.4 min, 14.5 min, and 94.4 min. The level of activity in the plasma was below the limit of detection 24 hrs after injection. During the study, no detectable activity was exhaled or excreted in the feces. By 24 hours, the cumulative urinary excretion was more than 99% of injected dose.

Figure 1: Percent of ^{14}C-DTPA Distribution



Absorption

Zn-DTPA is poorly absorbed by the GI tract. In animal studies, after oral administration, the absorption was approximately 5%.

Human or animal bioavailability comparisons for Zn-DTPA are not available after administration by inhalation and injection (intravenous, intramuscular or intraperitoneal). (See **CLINICAL PHARMACOLOGY, Clinical Trials**.)

Distribution

Following intravenous administration, Zn-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of Zn-DTPA penetrates into erythrocytes or other cells. No accumulation of Zn-DTPA in specific organs has been observed. There is little or no binding of the chelating agent by the renal parenchyma.

Metabolism

Zn-DTPA undergoes a minimal amount of metabolic change in the body.

Adverse Metabolic Effects: Only a very minor release of acetate groups has been demonstrated and splitting of ethylene groups has not been detected. Zn-DTPA results in minimal depletion of magnesium and manganese.

Elimination

Zn-DTPA is cleared from the plasma in the first few hours after dosing through urinary excretion by glomerular filtration. Renal tubular excretion has not been documented. In stool samples tested with radioactivity marked chelating agents, only a very small amount of radioactivity (<3%) was detected.

Renal Impaired and/or Compromised Liver Function Patients

Adequate and well-controlled pharmacokinetic and pharmacodynamic studies in renally impaired and/or hepatically impaired patients were not identified in the literature.

Both Zn-DTPA and its radioactive chelates are excreted by glomerular filtration. Impaired renal function may decrease their rates of elimination.

Clinical trials

Observational data was maintained in a U.S. Registry of patients with radiation contamination primarily from acute occupational exposure to plutonium, americium, and curium.

In 286 patients, bioassays were available to measure urinary radiation elimination after chelation therapy. Of these 286 patients, only 18 had matched pre- and post-chelator urine bioassay results available. The majority of these patients received Ca-DTPA as the initial component to their chelation therapy (see Ca-DTPA labeling). Ca-DTPA was administered as soon as possible after internal contamination with transuranium radionuclides (see Ca-DTPA labeing). When multiple chelator doses were administered over days, the standard of practice was to switch therapy to Zn-DTPA following an initial dose of Ca-DTPA, both chelators were considered equipotent 24 hours following exposure but An-DTPA was considered less toxic. There is very little clinical experience with the administration of Zn-DTPA as the initial dose of chelation therapy.

After initial treatment with Ca-DTPA, maintenance treatment was continued with daily 1-gram Zn-DTPA doses administered over a period of days, months or years, depending on the extent of internal contamination. Most patients were dosed daily after the initial dose. Over time the dosing interval decreased to weekly and monthly. Treatment was generally continued until the EEF approached 1. The longest treatment duration was approximately 4 years.

Similar increases in urinary radiation elimination were supported by data from the remaining patients in the U.S. Registry and from the literature.

INDICATIONS AND USAGE

Zn-DTPA is indicated for treatment of patients with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination.

CONTRAINDICATIONS

None known.

WARNINGS

Treatment with Zn-DTPA may decrease the levels of magnesium and manganesemeasured in the blood. The dose should not be divided because it increases the rate of endogenous metal depletion. (see **CLINICAL PHARMACOLOGY**, **Pharmacodynamics, *Metabolism*.**)

Zn-DTPA is administered to decrease internal contamination with certain transuranic radioactive isotopes. It does not treat the complications of radiation exposure. Patients contaminated with high levels of transuranium radioactive elements may develop radiation toxicity including bone marrow suppression with severe neutropenia and thrombocytopenia. As appropriate, supportive treatment for radiation toxicity should be given concomitantly with Zn-DTPA.

In radiologic emergencies, the radionuclide may not be known. Zn-DTPA may not bind to all radioactive elements. Patients contaminated with unknown or multiple radioactive elements may require concomitant treatment with other therapies in addition to Zn-DTPA (i.e., potassium iodide, Prussian blue).

PRECAUTIONS

General: *Metabolic*

Treatment over several months with Zn-DTPA could lead to depletion of body stores of endogenous metals (e.g., magnesium, manganese). These elements should be monitored routinely and, if appropriate, mineral or vitamin plus mineral supplements that contain zinc should be provided.

Information for Patients

Radioactive metals are known to be excreted in the urine, feces, and breast milk. In individuals

with recent internal contamination with these radioactive isotopes, Zn-DTPA treatment increases excretion of radioactivity in the urine (by as much as a factor of 100 over pre-treatment levels). This high concentration may persist for several days after Zn-DTPA is given. Appropriate safety measures should be taken to minimize radiation exposure to others. When possible, a toilet should be used instead of a urinal, and it should be flushed several times after each use. Spilled urine or feces should be cleaned up completely and patients should wash their hands thoroughly. If blood or urine comes in contact with clothing or linens, they should be washed separately. Patients should drink plenty of fluids and void frequently.

If patients are coughing, any expectorant should be disposed of carefully. Swallowing the expectorant should be avoided if possible.

Parents and child-care givers should take extra precaution in handling the urine, feces, and expectorants of pediatric patients to avoid any additional exposure to the either the caregiver or to the pediatric patient.

Nursing mothers should take extra precaution in disposing of breast milk. (See **PRECAUTIONS, Nursing Mothers.**)

Laboratory Tests

Serum electrolytes and essential metals should be closely monitored during Zn-DTPA treatment. mineral or vitamin plus mineral supplements that contain zinc should be given as appropriate. (See **WARNINGS** and **PRECAUTIONS**.)

Drug-Drug Interactions

Adequate and well-controlled drug-drug interaction studies in humans were not identified in the literature.

When an individual is contaminated with multiple radioactive isotopes, or when the radioactive contaminants are unknown, Zn-DTPA can be co-administered with other radioprotectants (e.g., Prussian blue, potassium iodide).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with Zn-DTPA to evaluate carcinogenesis, mutagenesis and impairment of fertility have not been performed.

Data for Zn-DTPA effects on spermatogenesis are not available.

Teratogenic Effects: *Pregnancy Category B*

There are no human pregnancy outcome data from which to assess the risk of Zn-DTPA exposure on fetal development. Reproduction studies have been performed in pregnant mice at doses up to 11.5 mmol/kg (31 times the recommended daily dose of 1 gram based on body surface area (BSA) adjusted dose) and have revealed no evidence of impaired fertility or harm to

the fetus due to Zn-DTPA. There was a slight reduction in the average birth weight. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. However, the risk of toxicity from untreated transuranium contamination is expected to be greater than any reproductive risk of treatment with Zn-DTPA.

Nursing Mothers

Studies to determine if Zn-DTPA is excreted in breast milk have not been conducted.

Radioactive elements are known to be excreted in breast milk. Women with known or suspected internal contamination with radioactive isotopes should not breast feed, whether or not they are receiving chelation therapy. Precautions should be taken when discarding breast milk. **(**See **PRECAUTIONS, Information for Patients**.)

Pediatric Use

The safety and efficacy of Zn-DTPA was established in the adult population and efficacy was extrapolated to the pediatric population on the basis of the comparability of pathophysiologic mechanisms. The dose is based on body size adjustment for an intravenous drug that is renally cleared.

ADVERSE REACTIONS

In the U.S. database, a total of 646 patients received at least one dose of either Ca-DTPA or ZN-DTPA. Of these, 62 received Zn-DTPA.

Of the patients that received Zn-DTPA, 49 /62 (65%) received multiple doses. The largest number of dosing treatments for Zn-DTPA was 574 doses delivered over 4 years.

Overall, the presence or absence of adverse events was recorded in 310/646 patients. Of these 19 (6.1%) patients reported at least one adverse event. The total number of recorded adverse events was 20. Of the 20 adverse events, 1 patient treated with Zn-DTPA reported headache, lightheadedness, and pelvic pain.

OVERDOSAGE

Overdose with Zn-DTPA has not been reported. Based upon the mechanism of action, symptoms of endogenous metal depletion may occur. (See **CLINICAL PHARMACOLOGY, Pharmacodynamics, *Metabolism*, WARNINGS and PRECAUTIONS**.)

DOSAGE AND ADMINISTRATION

THE MAIN OBJECTIVE OF CHELATION TREATMENT IS TO REDUCE INTERNAL RADIOACTIVE CONTAMINATION BY INCREASING THE RATE OF EXCRETION AND REDUCING TISSUE DEPOSITION.

Treatment should be started as soon as possible after suspected or known contamination. However, even when treatment cannot be started right away, patients should be given chelation treatment as soon as it becomes available. Chelation treatment is still effective even after time has elapsed following exposure..

If contamination with isotopes other than plutonium, americium, or curium, or unknown isotopes is suspected, additional therapies may be needed (e.g., Prussian blue, potassium iodide).

The chelating effect of Zn-DTPA is greatest when the radionuclide is still circulating or is in interstitial fluids. The effectiveness of chelation decreases with time following internal contamination as the radionuclide becomes sequestered in liver and bone.

Patients should drink plenty of fluids and void frequently to promote dilution of the radioactive chelate in the urine and minimize radiation exposure directly to the bladder.

Initial dose

It is preferable to administer Ca-DTPA, if available, as the initial dose during the first 24 hours after contamination because Ca-DTPA is more effective than Zn-DTPA during this time period. After 24 hours Zn-DTPA and Ca-DTPA are equally effective.

Adults and adolescents: A single 1.0 gram initial dose of Zn-DTPA administered intravenously.

Pediatrics (less than 12 years of age): A single initial dose of 14 mg/kg administered intravenously. The maximum single loading dose should not exceed 1.0 gram.

Renally impaired patients: No dose adjustment is needed. However, in heavily contaminated patients dialysis may be used to increase the rate of elimination. High efficiency high flux dialysis is recommended. Because dialysis fluid will become radioactive, radiation precautions must be taken to protect personnel, other patients, and the general public.

Maintenance Treatment

Adults and adolescents: The recommended maintenance dose of Zn-DTPA is 1.0 gram once a day administered intravenously.

Pediatrics (less than 12 years of age): The recommended maintenance dose of Zn-DTPA is 14 mg/kg once a day administered intravenously. The maximum daily dose should not exceed 1.0 gram per day.

Renally impaired patients: No dose adjustment is needed. However, in heavily contaminated patients, dialysis may be used to increase the rate of elimination. High efficiency high flux dialysis is recommended. Because dialysis fluid will become radioactive, radiation precautions must be taken to protect personnel, other patients, and the general public.

Treatment should continue for a minimum of 30 days and then the patient should be

reassessed for the amount of residual whole body radioactivity. The duration of treatment after exposure is dictated by the level of contamination and the judgement of the attending physician. Before, during, and after chelation therapy, pertinent measurements for radioactivity should be made to help determine when to terminate treatment.

Methods of Administration

The intravenous route is recommended. Zn-DTPA solution (1-gram in 5 mL) should be administered either with a slow intravenous push over a period of 3-4 minutes or by intravenous infusion diluted in 100-250 mL of D_5W, Ringers Lactate, or Normal Saline.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Monitoring

When possible, obtain baseline blood and urine samples (CBC with differential, BUN, serum chemistries, and electrolytes, urinalysis and blood and urine radioassay) before initiating treatment.

To establish an elimination curve, a quantitative baseline estimate of the total internalized transuranium element(s) and measures of elimination of radioactivity should be obtained by appropriate whole-body counting, by bioassay (e.g., biodosimetry), or fecal/urine sample whenever possible.

During treatment, the following information should be collected:

- Measurements of the radioactivity in blood, urine, and fecal samples weekly to monitor the transuranium contaminant elimination rate.
- Record any adverse events from Zn-DTPA.
- CBC with differential, BUN, serum chemistries and electrolytes, and urinalysis measurements should be monitored regularly. (See **CLINICAL PHARMACOLOGY, Pharmacodynamics,** ***Metabolism***.)

HOW SUPPLIED

Each ampule contains 1- gram (2.0 millimoles) of Zn-DTPA in X mL of sterile aqueous solution.

NDC# XXXXX-XXX-XX

Storage

Store at XX-XX°C (YY-YY°F) [See USP Controlled Room Temperature]. Protect from light.

COLLECTION OF PATIENT TREATMANT DATA

To develop long-term response data and information on the risk of developing late malignancy, detailed information on patient treatment should be provided to the manufacturer. These data should include a record of the radioactive body burden and bioassay results at defined time intervals, a description of measurement methods to facilitate analysis of data, and adverse events.

Questions regarding the use of Zn-DTPA for the treatment of contamination with transuranium elements may be referred to:

(Insert Name and contact information)……